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Review of Experimental Carcinogenesis by Compounds Related to Vinyl Chloride

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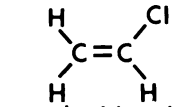
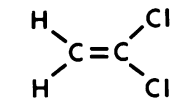
The experimental carcinogenesis results on six compounds related to vinyl chloride are reported. Vinylidene chloride, given by inhalation, was carcinogenic in male CD-1 mice, male CD rats, Sprague-Dawley rats and male Swiss mice. Trichloroethylene, given by gavage and inhalation, was carcinogenic in the B6C3F1 mice. When given by gavage, perchloroethylene was carcinogenic in the B6C3F1 mice, and dichloroethane was carcinogenic in Osborne-Mendel rats and B6C3F1 mice. Dibromoethane, given by gavage and inhalation, was carcinogenic in B6C3F1 mice, F344 rats and Osborne-Mendel rats. Finally, epichlorohydrin was carcinogenic in male Sprague-Dawley rats and B6C3F1 mice.

Introduction

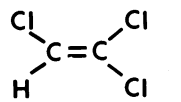
Since the carcinogenicity of vinyl chloride (VC) was demonstrated in experimental (*1*) and epidemiologic studies (*2*), data on the potential carcinogenicity of vinyl chloride structural analogs and related compounds have been increasing. This paper will attempt to review the experimental carcinogenicity data on a number of these compounds, while another paper (*3*) will discuss the epidemiologic results.



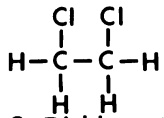
Vinyl chloride
VC



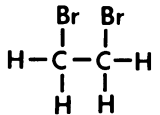
Vinylidene chloride
VDC



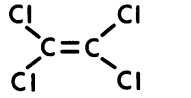
Trichloroethylene
TCE



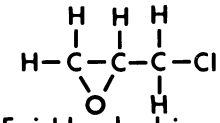
1,2-Dichloroethane
DCE



1,2-Dibromoethane
DBE



Tetrachloroethylene
PCE



Epichlorohydrin
EPC

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Results

Vinylidene Chloride (VDC)

A summary of some of the carcinogen bioassays of vinylidene chloride is given in Table 1. The strongest evidence of a carcinogenic effect was in a bioassay involving Swiss mice performed by Maltoni et al. (*4, 5*). In this study, 24/150 dosed male mice had kidney tumors as compared to 0/190 in the controls. In the study by Lee et al. (*6, 7*), dosed CD-1 mice and CD rats had two or three liver angiosarcomas. Since this type of tumor was induced by vinyl chloride in humans and rodents and the study was terminated after only one year, the results are viewed as biologically significant. In an inhalation study in Sprague-Dawley rats by Maltoni et al. (*4, 5*), increases in mammary gland tumors in the dosed animals were reported. However, these incidences did not follow a dose-response relationship.

In contrast to these positive studies, a number of nonpositive two-year carcinogen bioassay studies have been reported (*6-9*). Most notable is this initial report that preliminary evaluations of vinylidene chloride in a two-year National Toxicology Program (NTP)/NCI bioassay of Fischer 344 rats, given at 2-10 mg/kg of body weight and of B6C3F1 mice, given at 1-5 mg/kg of body weight, did not indicate any significant increased incidences of tumors in the dosed animals as compared to controls.

Trichloroethylene (TCE)

A summary of some of the carcinogen bioassays of trichloroethylene is reported in Table 2. In B6C3F1 mice, this compound, given by gavage, was found to be carcinogenic, inducing hepatocellular tumors (*10*). In confirmation of this finding, an inhalation study in B6C3F1 mice, performed by Biotest Laboratories, gave similar results (*11*).

Bioassays of TCE were nonpositive in two strains of rats, the Sprague-Dawley and Osborne-Mendel (*10-12*). Additional NTP/NCI carcinogen bioassays are under way in five strains of rat and the B6C3F1 mice to examine species and strain differences.

Tetrachloroethylene (Perchloroethylene) PCE

The carcinogen bioassay results of testing PCE are given in Table 3. In B6C3F1 mice, this compound, given by gavage, was carcinogenic inducing hepatocellular tumors.

Studies in two strains of rats, Osborne-Mendel and Sprague-Dawley, produced no carcinogenic effects (*13-14*). Additional carcinogen bioassays in four strains of rats and the female B6C3F1 mice are currently underway at NTP/NCI.

1,2-Dichloroethane (DCE)

The experimental carcinogenicity results of testing DCE are given in Table 4. In B6C3F1 mice, the

Table 1. Bioassays of vinylidene choride (VDC).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose ppm or mg/kg[c]	Dosing period (duration), wk	Group size	Target site (tumor incidences)[d]	Reference
Mouse, CD–1	Inhal	M	55	52D(52)	36	Liver, hemangiosarcoma	(*6,7*)
			0	"	36	(2/35 0/26)	
		F	55	52D(52)	36	Liver, hemangiosarcoma	
			0	"	36	(1/35 0/36)	
Rat, CD	Inhal	M	55	52D(52)	36	Hemangiosarcoma	(*6,7*)
			0	"	36	(2/36 0/35)	
		F	55	52D(52)	36	NSC	
			0	"	36		
Rat, Spr-Daw	Inhal	M	150	52D(life)	60	NSC	(*4,5*)
			100	" "	30		
			50	" "	30		
			25	" "	30		
			10	" "	30		
			0	" "	100		
		F	150	52D(life)	60	Mammary gland	
			100	" "	30	(nondose response)	
			50	" "	30		
			25	" "	30		
			10	" "	30		
			0	" "	100		

Table 1 (cont.)

Species/Str[a]	Route (vehicle)[b]	Sex	Dose ppm or mg/kg[c]	Dosing period (duration), wk	Group size	Target site (tumor incidences)[d]	Reference
Mouse, Swiss	Inhal	M	25	52D(life)	150	Kidney	(*4*, *5*)
			10	" "	30	(24/150 0/190)	
			0	" "	190		
		F	25	52D(life)	150	NSC	
			10	" "	30		
			0	" "	190		
Rat, Spr-Daw	Gav (Olive oil)	M	20	52D(life)	50	NSC	(*4*, *5*)
			10	" "	50		
			5	" "	50		
			0	" "	50		
		F	20	52D(life)	50	NSC	
			10	" "	50		
			5	" "	50		
			0	" "	50		
Hamster, Chin	Inhal	M	25	52D(life)	30	NSC	(*4*, *5*)
			0	" "	30		
		F	25	52D(life)	30	NSC	
			0	" "	30		
Mouse B6C3F1 (NCI)	Gav (Corn oil)	M	10	(103)	50	NSC[e]	
			2	"	50		
				"	50		
		F	10	(103)	50	NSC[e]	
			2	"	50		
			0	"	50		
Rats, F344 (NCI)	Gav (Corn oil)	M	5	(103)	50	NSC[e]	
			1	"	50		
			0	"	50		
		F	5	(103)	50	NSC[e]	
			1	"	50		
			0	"	50		
Rat, Spr-Daw	Inhal	M	75	78D(104)	86	NSC	(*8*)
			25	"	85		
			0	"	86		
		F	75	78D(104)	86	NSC	
			25	"	84		
			0	"	88		
Rat, Spr-Daw	Water	M	200	(104)	47	NSC	(*8*)
			100	"	48		
			60	"	48		
			0	"	80		
		F	200	(104)	47	NSC	
			100	"	48		
			60	"	48		
			0	"	80		
Rat, Wistar	Inhal	M	200–100	52D(104)	51	NSC	(*9*)
			0	"	30		
		F	200–100	52D(104)	23	NSC	
			0	"	30		
Rat, Spr-Daw	Inhal	M	100	52D(104)	30	NSC	(*9*)
			75	" "	16		
			0	" "	30		
		F	100	52D(104)	30	NSC	
			75	" "	21		
			0	" "	30		

[a]Chin = Chinese hamster; F344 = Fischer 344 rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]Units: ppm for inhalation; mg/kg for other routes.
[d]NSC = Not shown to be carcinogenic.
[e]Preliminary results.

compound, given by gavage, was carcinogenic, inducing lung tumors in both sexes and mammary gland and uterus tumors in dosed female animals (*15*). The chemical was also carcinogenic in Osborne-Mendel rats, giving forestomach tumors and extrahepatic hemangiosarcomas in both sexes, subcutaneous fibromas in the males and mammary gland tumors in the females (*15*).

In contrast, a preliminary report by Maltoni (*12*) indicated that DCE was not shown to be carcinogenic in an inhalation study with Swiss mice and Sprague-Dawley rats. Since there were strain and

Table 2. Bioassays of trichloroethylene (TCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse B6C3F1[d]	Gav (Corn oil)	M	2339	78D(90)	50	Liver, hepatocellular (31/48 26/50 1/20)	(*10*)
			1169	" "	50		
			0	" "	20		
		F	1739	78D(90)	50	Liver, hepatocellular 11/47 4/50 0/20)	
			869	" "	50		
			0	" "	20		
Mouse B6C3F1[d]	Inhal	M	600 ppm	(104)	100	Liver, hepatocellular (43/97 31/100 28/95 18/99)	(*11*)
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
		F	600 ppm	(104)	100	Liver, hepatocellular (13/99 9/94 4/100 6/99)	
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
Rat, Osb-Mdl[d]	Gav (Corn oil)	M	1097	78D(110)	50	NSC	(*10*)
			549	" "	50		
			0	" "	20		
		F	1097	78D(110)	50	NSC	
			549	" "	50		
			0	" "	20		
Rat, Spr-Daw	Gav (Olive oil)	M	250	52D(140)	30	NSC	(*12*)
			50	" "	30		
			0	" "	30		
		F	250	52D(140)	30	NSC	
			50	" "	30		
			0	" "	30		
Rat, Charles River[d]	Inhal	M	600 ppm	(104)	100	NSC	(*11*)
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
		F	600 ppm	(104)	100	NSC	
			300 ppm	"	100		
			100 ppm	"	100		
			0	"	100		
Rat, Marshall (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress St. 2/79	
			500	"	50		
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, ACI (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress St. 2/79	
			500	"	50		
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, F344 (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress St. 6/78	
			500	"	50		
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		

Table 2 (cont.)

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Rat, Osb-Mdl (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 12/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, August (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			500	"	50	St. 10/79	
			0	"	50		
		F	1000	(110)	50	Assay still in progress	
			500	"	50		
			0	"	50		
Rat, B6C3F1 (NCI)	Gav (Corn oil)	M	1000	(110)	50	Assay still in progress	
			0	"	50	St. 6/78	
		F	1000	(110)	50	Assay still in progress	
			0	"	50		

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage, Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.
[d]With 0.09% epichlorohydrin.

dose differences as well as route of administration differences between the NTP/NCI and Maltoni studies, the causes of the differences in the experimental results are not readily apparent.

1,2-Dibromoethane (DBE)

The results of some carcinogen bioassays on DBE are given in Table 5. In bioassays on B6C3F1 mice and Osborne-Mendel rats, DBE given by gavage was carcinogenic, inducing multiple tumors in each species and sex. There were not only chemically induced tumors at the site of application (forestomach tumors) but also tumors distant from the site of application (lung tumors in mice and extrahepatic hemangiosarcomas in male rats and hepatocellular tumors in female rats) (*16*).

In addition, a preliminary analysis of an inhalation study of DBE performed by NTP/NCI indicates that nasal cavity tumors were found in dosed rats and dosed female mice. Furthermore, elevated incidences of lung tumors were found in the dosed mice as well as elevated incidences of mammary gland tumors in dosed females of each test species. Mesotheliomas were also induced by DBE in male rats.

Epichlorohydrin (EPC)

The bioassay results on epichlorohydrin are given in Table 6. Recently, this compound, given by inhalation, was found to be carcinogenic inducing nasal cavity tumors in male rats (*17*). In addition, experiments by Van Duuren (*18-19*) indicated that EPC was an initiator in a two-stage study and induced local sarcomas by subcutaneous injection. addition more comprehensive epidemiological studies involving the manufacture, production and use of these compounds should be undertaken.

A summary of some of the bioassay results for each compound by species/strain is given in Table 7.

Discussion

The data on these compounds can generate some interesting points for discussions, such as the probable mechanism of some of these compounds, the controversy over TCE results and suggestions for future action.

In the first case, studying the summary table indicates that the compounds (DBE, DCE, and EPC) which are proposed to alkylate directly, gave forestomach tumors when given by gavage or nasal cavity tumors when given by inhalation while the compounds which are proposed to require metabolic activation did not produce these types of tumors. One can envision that these compounds, due to their alkylating ability and their ability to induce site of application tumors, are direct-acting carcinogens. Two of these former compounds, DBE and

Table 3. Bioassays of perchloroethylene (PCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse B6C3F1	Gav (Corn oil)	M	1072	78D(90)	50	Liver, hepatocellular	(*13*)
			536	" "	50	(27/48 32/49 2/20)	
			0	" "	20		
		F	772	78D(90)	50	Liver, hepatocellular	
			386	" "	50	(19/48 19/48 0/20)	
			0	" "	20		
Rat, Osb-Mdl	Gav (Corn oil)	M	941	71D(110)	50	NSC	(*13*)
			471	" "	50		
			0	" "	20		
		F	949	71D(110)	50	NSC	
			474	" "	50		
			0	" "	20		
Rat, Spr-Daw	Inhal (Corn oil)	M	600 ppm	52D(135)	96	NSC	(*14*)
			300 ppm	" "	96		
			0	" "	96		
		F	600 ppm	52D(135)	96	NSC	
			300 ppm	" "	96		
			0	" "	96		
Rat, Sherman (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress	
			375	"	50	St. 2/78	
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, Wistar (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress	
			375	"	50	St. 11/78	
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, Long-Evans (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress	
			375	"	50	St. 7/78	
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, F344 (NCI)	Gav (Corn oil)	M	750	(103)	50	Assay still in progress	
			375	"	50	St. 9/78	
			0	"	50		
		F	750	(103)	50	Assay still in progress	
			375	"	50		
			0	"	50		
Rat, B6C3F1 (NCI)	Gav (Corn oil)	F	200	(103)	100	Assay still in progress	
			100	"	100		
			50	"	100		
			25	"	100		
			0	"	100		

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.

DCE, also induced tumors distant from the site of application. This fact may be an important point in the controversy over TCE.

This controversy stems from the fact that the results on TCE indicated that the mice studies were positive while the rat studies showed the chemical did not produce a carcinogenic effect. There have been several explanations. It has been postulated that epichlorohydrin, used as a stabilizer in the TCE tested, is responsible for the positive effect, not TCE (*21*). The NCI Technical report on TCE (*10*) indicated that there was 0.09% EPC in

Table 4. Bioassays of 1,2-dichloroethane (DCE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Mouse, B6C3F1	Gav (Corn oil)	M	195	78D(91)	50	Lung	(15)
			97	" "	50	(15/48 1/47 0/19)	
			0		20		
		F	299	78D(91)	50	Lung (15/48 7/50 1/20)	
			149	" "	50	Mammary gland (7/48 9/50 0/20)	
			0		20	Uterus (5/47 5/49 0/20)	
Rat, Osb-Mdl	Gav (Corn oil)	M	95	69D(110)	50	Forestomach (9/50 3/50 0/10)	(15)
			47	" "	50	Hemangiosarcoma (7/50 9/50 0/20)	
			0		20	SQ Fibroma (6/50 5/50 0/20)	
		F	95	69D(93)	50	Mammary gland	
			47	(110)	50	(18/50 1/50 0/20)	
			0		20		
Mouse, Swiss	Inhal	M	250–150 ppm	(life)	90	NSC[d]	(12)
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	180		
		F	250–150 ppm	(life)	90	NSC[d]	
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	180		
Rat, Spr-Daw	Inhal	M	250–150 ppm	(life)	90	NSC[d]	(12)
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	90/180		
		F	250–150 ppm	(life)	90	NSC[d]	
			50 ppm	"	90		
			10 ppm	"	90		
			5 ppm	"	90		
			0	"	90/180		

[a]Osb-Mdl = Osborne-Mendel rat; Spr-Daw = Sprague-Dawley rat.
[b]Gav = gavage; Inhal = inhalation.
[c]NSC = Not shown to be carcinogenic.
[d]Preliminary results.

the TCE. The doses of TCE were about 2000-1000 mg/kg of body weight, corresponding to less than 2 mg/kg of body weight of epichlorohydrin. If epichlorohydrin is the active agent, one might expect forestomach tumors from a gavage study because of its alkylating ability. However, the target site in the mice is the liver. In addition, if epichlorohydrin is the carcinogen, then why are the results negative in the rat? Direct-acting carcinogens, like epichlorohydrin, are less likely to show such a species difference than compounds which would require metabolic activation, such as TCE itself. Thus, an alternative explanation is that there is a species difference reflecting some type of metabolic or target site sensitivity difference between the species.

The answer may be forthcoming. NTP/NCI is testing TCE without EPC in the B6C3F1 mice and five strains of rat. If EPC is the active compound, the mice study should not show a carcinogenic effect. However, if TCE is the active agent then the B6C3F1 mouse study should be positive. The results in the rats will also give insight into whether there is a species or a species/strain difference for TCE. Similar types of studies are also underway with PCE. In addition, Maltoni has indicated that he has started bioassays on TCE with B6C3F1 mice and Swiss mice.

With the possible resolution of the TCE issue, there still remains the differences in experimental results involving vinylidine chloride (VDC). The results in VDC may indicate that there are important species and strain differences. As a consequence, this compound may be an ideal candidate for studying species/strain differences systematical-

Table 5. Bioassays of 1,2-dibromethane (DBE).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose, mg/kg	Dosing period (duration), wk	Group size	Target site (tumor incidences)	Reference
Mouse B6C3F1	Gav (Corn oil)	M	107	53D(78)	50	Forestomach (29/49 45/50 0/20)	(*16*)
			62	" "	50	Lung (10/47 4/45 0/20)	
			0	"	20		
		F	107	53D(90)	50	Forestomach (28/50 46/49 0/20)	
			62	" "	50	Lung (6/46 11/43 0/20)	
			0	(60)	20		
Rat, Osb-Mdl	Gav (Corn oil)	M	41	34D(49)	50	Forestomach (33/50 45/50 0/20)	(*16*)
			38	47D"	50	Hemangiosarcoma	
			0	(63)	20	(4/50 11/50 0/20)	
		F	39	44D(61)	50	Forestomach (29/50 40/50 0/20)	
			37	57D"	50	Liver, hepatocellular	
			0	(63)	20	(5/48 1/47 0/20)	
Mouse B6C3F1 (NCI)	Inhal	M	40 ppm	(103)	50	Lung (19/46 3/48 0/41)[c]	
			10 ppm	"	50		
			0	"	50		
		F	40 ppm	(103)	50	Nasal cavity (6/50 0/50 0/50)[c]	
			10 ppm	"	50	Mammary gland (8/50 14/50 2/50)[c]	
			0	"	50	Lung (37/50 5/49 1/49)[c]	
Rat, F344 (NCI)	Inhal	M	40 ppm	(103)	50	Nasal cavity (28/50 20/50 0/50)[c]	
			10 ppm	"	50	Mesothelioma	
			0	"	50	(25/50 7/50 1/50)[c]	
		F	40 ppm	(103)	50	Nasal cavity (29/50 20/50 0/50)[c]	
			10 ppm	"	50	Mammary gland	
			0	"	50	(24/50 29/50 4/50)[c]	

[a]F344 = Fischer 344 rat; Osb-Mdl = Osborne-Mendel rat.
[b]Gav = gavage; Inhal = inhalation.
[c]Preliminary results.

Table 6. Bioassays of epichlorohydrin (EPC).

Species/Str[a]	Route (vehicle)[b]	Sex	Dose	Dosing period (duration), wk	Group size	Target site (tumor incidences)[c]	Reference
Rat, Spr-Daw	Inhal	M	100 ppm	6D(life)	140	Nasal cavity	(*17*)
			30 ppm	(life)	100	(15/140 2/100 0/100 0/50)	
			0	"	100		
					50		
Mouse, ICR/Ha Swiss	SC	F	1 mg in 0.1 ml tricaprylin wkly	(life)	50	Local sarcomas (2/50 0/50)	(*19*)
Mouse, ICR/Ha Swiss	SC	F	1 mg in 0.05 ml tricaprylin wkly	(life)	50	Local sarcomas (7/50 1/50)	(*18*)
Mouse	Skin		1 mg in 0.1 ml acetone then 2.5 g phorbol myristate[c]	1 dose 55D	30	Initiator (10/30 3/30)	(*18*)
Mouse, C3H	Skin	—	1 Br	(life)	40	NSC	(*20*)
Mouse, ICR/Ha	Skin	F	2 mg in 0.1 ml acetone 3/wk	57D(57)	50	NSC	(*18*)
Mouse, ICR/Ha	IP	F	1 mg in 0.05 ml tricaprylin wkly	(64)	30	NSC	(*18*)

[a]Spr-Daw = Sprague-Dawley rat.
[b]IP = intraperitoneal injection; SC = subcutaneous injection; Skin = skin painting.
[c]NSC = Not shown to be carcinogenic.

Table 7. Summary of bioassay results on vinyl chloride analogs and related compounds for some tumor sites.

	VC	VDC	TCE	PCE	DCE	DBE	ECH
Hemangio-sarcoma	SD Rat-G Mouse-I[a] Rat-I[a]	m-CD-1 Mouse-I m-CD Rat-I			m-OM Rat-G	m-OM Rat-G	
Lung tumors	Mouse-I[a] Rat-I[a]				B6C3P1-G	B6C3F1-G B6C3F1-G[b]	
Mammary gland tumors (females)	Mouse-I[a]	SD Rat-I			OM Rat-G B6C3F1-G	F344 Rat-I[b] B6C3F-I[b]	
Kidney tumors		m-Sw Mouse-I					
Hepatocellular tumors			B6C3F1-G B6C3F1-I	B6C3F1-G		f-OM Rat-G	
Forestomach tumors					m-OM Rat-G	OM Rat-G B6C3F1-G	
Nasal cavity tumors						F344 Rat-I[b] f-B6C3F1-I[b]	m-SD Rat-I
Local sarcoma							f-ICR/Ha Sw Mouse-SP
NSC		F344 Rat-G[b] B6C3F1-G[b] Wis Rat-I Ch Ham-I SD Rat-W SD Rat-I SD Rat-G	OM Rat-G SD Rat-G CR Rat-I	OM Rat-G SD Rat-G	SD Rat-I Sw Mouse-I		

[a]Effect seen in at least two strains.
[b]Preliminary results on NTP/NCI studies.

ly. In addition, the differences in the NCI and Maltoni studies on DCE could be the source for additional research.

From an examination of Table 7, the compounds with positive results in multiple species yielding multiple tumor sites are the direct acting carcinogens, DBE and DCE. (EPC has not been tested extensively yet.) This strong evidence in experimental carcinogenesis should, at least, trigger measures to decrease exposure to these compounds. In addition more comprehensive epidemiological studies involving the manufacture, production and use of these compounds should be undertaken.

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